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A randomized comparison of extended-release naltrexone with or without patient navigation vs enhanced treatment-as-usual for incarcerated adults with opioid use disorder

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Abstract

The high prevalence of opioid use among justice-involved adults make jails an exceptional setting to initiate opioid use disorder (OUD) treatment, but optimal strategies for delivering these interventions are still not well understood. The objective of this study was to conduct a randomized controlled trial to assess the effectiveness of extended-release naltrexone (XR-NTX, Vivitrol®; Alkermes Inc) alone or in conjunction with patient navigation (XR-NTX+PN) for jail inmates with OUD. We randomized a sample of 135 sentenced jail inmates with moderate to severe OUD to (1) XR-NTX only; (2) XR-NTX+PN; or (3) enhanced treatment-as-usual (ETAU) with drug education, each initiated prior to release from jail. We scheduled follow-up data assessments at 1, 3, 6, and 12 months post-release. Primary outcomes were opioid use (based on Timeline Followback Interview and Addiction Severity Index) and meeting CIDI DSM-5 criteria for OUD 6 months postrelease. We also measured treatment adherence, HIV risk, and recidivism. XR-NTX participants received a mean of 2.26 of 7 possible injections compared to XR-NTX+PN participants, who received a mean of 2.93 injections (Cohen's $d=0.33$, 95% CI: -0.09 to 0.74). Thirty-six percent of patients in XR-NTX+PN attended at least one postrelease PN session. We found no significant differences by study condition six months after release from jail for the

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primary outcomes of any opioid use (ETAU: 17%, XR-NTX: 16%, XR-NTX+PN: 29%) and past 30-day OUD (ETAU: 8%, XR-NTX: 11%, XR-NTX+PN: 10%). Secondary outcomes of rearrest and HIV risk also were similar across groups, with the exception of lower sex-related HIV risk among those in the XR-NTX condition at 12 months. This study did not show superior outcomes of XR-NTX or XR-NTX+PN with regard to opioid use or recidivism outcomes, relative to ETAU. It did, however, highlight the difficulties with adherence to XR-NTX and PN interventions in OUD patients initiating treatment in jail.

Keywords

Opioid dependence; Jail inmates; Experimental; Injectable naltrexone; Extended release naltrexone

1 Introduction

In many countries, including the United States, the high prevalence of opioid use among justice-involved adults make jails an exceptional setting to identify those with opioid use disorder (OUD) and initiate treatment. The 2017 National Survey on Drug Use and Health estimated that 0.8 percent of the general U.S. population currently meets criteria for OUD (SAMHSA, 2018), whereas these criteria are met by approximately a quarter of jail inmates (Proctor, Hoffmann, & Raggio, 2019). Moreover, the risk of death among parolees during the two weeks following release from prison is nearly 13 times greater than among individuals of similar demographic background, with drug overdose being the leading cause of death (Binswanger et al., 2015).

Naltrexone, an opioid receptor antagonist, blocks the euphoric effects of heroin and other opioids. This characteristic has fostered growing acceptance of naltrexone by correctional authorities who are reluctant to provide opioid agonist treatment out of concerns that it will be diverted (Farabee, 2006). A depot formulation of naltrexone was developed to overcome the issue of poor adherence to oral preparations for daily use. Extended-release naltrexone (XR-NTX, Vivitrol® with 380mg naltrexone delivered intramuscularly every four weeks; Alkermes, Inc.) was developed to provide long-acting pharmacotherapy for one month per dose. An estimated 200 jails in 40 states now offer XR-NTX at the point of re-entry to jail inmates with OUD (Vestal, 2018).

Several trials of XR-NTX have shown it to have promising effects on opioid use. In a double-blind, placebo-controlled experiment in Russia, Krupitsky et al. (2011) randomized 250 patients to XR-NTX or a placebo condition and found significantly lower rates of opioid use and opioid craving among those in the intervention group over a 6-month period. An open-label trial of justice-involved individuals with OUD (N=308) showed that those randomized to receive XR-NTX had a one-third reduction in opioid use and twice the median time to relapse of those in the control condition at the 6-month follow-up, but the differences had dissipated by 12 months (Lee et al., 2016). It is important to note that both of these trials were based on community samples, so the results do not reflect the growing practice of initiating XR-NTX treatment with incarcerated individuals prior to release, with ongoing treatment available thereafter. Lee and colleagues (Lee et al., 2015) did conduct a

small (N=34) pilot study of XR-NTX with a prerelease jail sample and found that rates of opioid use and relapse one month later were approximately half that of the control participants. Though the results were generally promising, these studies showed a steep decline in XR-NTX adherence over the course of the trials and, in the latter two studies using criminal justice samples, no effect on criminal recidivism.

The process of returning to the community following a jail or prison term is often fraught with challenges, including, but not limited to, substance misuse (Turner, 2018). As a result, there has been growing interest in using peer or patient navigators to improve access to health services and to help overcome related barriers to reentry.

1.1 Patient navigation (PN)

PN was originally developed in the 1990s to help cancer patients overcome barriers to obtaining treatment services (Wells et al, 2008). In the current study, patient navigators assisted participants in accessing care and overcoming practical barriers following release from jail, such as transportation and healthcare enrollment. Binswanger et al. (2007) found that former prison inmates who were randomly assigned to receive PN and facilitated enrollment into indigent healthcare had fewer hospitalizations than those randomized to a control condition (referral for discounted indigent care only). Similarly, in a randomized comparison of HIV-infected individuals (N=270) leaving jail, those receiving PN-enhanced case management were more likely to enter and remain in HIV care than those receiving case management alone (Myers et al., 2018). Thus, the current study had two primary aims: (1) to test the effectiveness of XR-NTX compared to enhanced treatment-as-usual for opioid dependent inmates in a county jail, and (2) to test whether patient navigation improved outcomes over XR-NTX alone.

2 Methods

This was an open-label trial designed to examine the feasibility and effectiveness of XR-NTX for OUD, alone or in conjunction with PN, relative to enhanced treatment-as-usual (ETAU) in a jail sample (a more detailed description of the protocol can be found in Farabee et al. [2016]). Participants in the XR-NTX and XR-NTX+PN groups received standard medical management. Before discharge from jail, participants randomized to either of the two medication conditions received XR-NTX and then received subsequent injections every four weeks for up to six additional months. Those in the XR-NTX+PN condition were scheduled to meet with a patient navigator before discharge and regularly (weekly in the first month; biweekly in months 2–3) after release to discuss barriers to treatment, possible treatment program participation following release, and to address social support and other participant needs. We provided participants randomized to the ETAU with a fact sheet regarding opioid overdose and a referral list of providers of medications for opioid use (MOUD) in the community. Prior to data collection, the Institutional Review Boards at the University of New Mexico and University of California, Los Angeles, approved the study.

2.1 Study site

We recruited participants from a county jail—the Bernalillo County Metropolitan Detention Center (MDC)—in Albuquerque, New Mexico.

2.2 Interventions

We randomized patients to receive XR-NTX with or without PN, or to receive ETAU without medication.

2.2.1 XR-NTX—Participants in both of the medication conditions received XR-NTX (in the form of Vivitrol) as a gluteal IM injection (380 mg) administered every four weeks, after a naloxone challenge. We scheduled medical management visits to occur twice-monthly during months 1–3, and monthly during months 4–6, and we provided XR-NTX injections monthly for up to six months following the initial injection in jail (follow-up injection could also occur in jail, if the participant returned to the MDC and wished to continue treatment). During these visits, participants met with study physicians and other study personnel to discuss adverse events, medication effects and side effects, and other pertinent issues in keeping with sound medical practice. They also provided a urine specimen if not incarcerated. At the end of the intervention phase, we referred participants expressing a desire to continue receiving injectable naltrexone to community care for re-assessment and continued treatment.

2.2.2 Patient navigation (PN)—In addition to receiving XR-NTX, we assigned participants in the XR-NTX+PN condition a patient navigator, who was employed by the research grant. The patient navigator provided one-on-one assistance to surmount barriers associated with reentry into the community and adherence to medical management. Following an in-person visit in jail, the patient navigator made efforts to have contact (in person or by phone) with participants at least once per week. During months 2 and 3, contact attempts were less frequent for most participants, but they were supposed to occur at least once every two weeks.

2.3 Participants

Participants were 135 jail inmates in the Bernalillo County Metropolitan Detention Center who (1) were at least 18 years of age; (2) met criteria for DSM-5 OUD; (3) were expected to be detained for at least 30 days; (4) had an expected release date within one year; and (5) planned to reside in the area after release. We excluded individuals if they (1) had a medical (e.g., liver failure, congestive heart failure) or psychiatric condition (e.g., suicidal ideation, psychosis) that would make participation unsafe in the judgment of the medical staff; (2) had chronic pain with plans to undergo pain treatment/therapy; (3) had known sensitivity to naltrexone or naloxone; (4) had participated in an investigational drug study within 30 days prior to screening; (5) were a nursing or pregnant female, or did not agree to use a medically acceptable form of birth control or complete abstinence (when applicable); (6) had a pending legal action that could prohibit continued participation for the 24-week intervention period; or (7) had a current pattern of alcohol, benzodiazepine, or other depressant or sedative hypnotic use, as determined by the study physician, that would preclude safe participation in the study. We also excluded participants if they did not show comprehension of the study by

passing several informed consent quiz questions. The baseline target sample of 150 participants with 50 participants per condition was based on an assumed final aggregate sample of approximately 120 participants (assuming 10–20% dropout). This would permit detection of a medium-large effect size ($\sim .60$) between conditions (at $\sim .70$ power).

We provided incentives in the form of gift or rechargeable debit cards for participating in screening (\$25); medical management (\$20 per visit for up to 9 visits); and research assessment visits at months 1, 3, and 6 (\$40 per visit) and 12 (\$80). Thus, participants in the medication conditions could receive up to \$405; participants in ETAU could receive up to \$225.

2.4 Assessments

We measured opioid use using the Addiction Severity Index (ASI) and the Timeline Follow-Back Interview (TLFB) and analyzed both as a binary outcome (any use vs. no use) and as a continuous measure of outcome (percentage of days of self-reported opioid use, adjusting for days at risk by excluding days that participants were incarcerated). At baseline, the TLFB assessed opioid use extending 90 days prior to the last date of opioid use before incarceration. At follow-ups, the TLFB assessed opioid use days continuously from the date the previous TLFB assessment ended. We collected urine samples at medical management visits (for the two medication groups). The protocol called for urine samples to be collected at each follow-up visit for all study participants. However, we collected urine samples only from participants who came to the research center for follow-ups. Research staff were not allowed to collect urine specimens from participants interviewed in the jail, and it was logistically difficult to collect urines from participants interviewed in public sites, such as restaurants or libraries. We determined OUD using the CIDI-2 Substance Abuse Module for Opioids, which assessed past-year DSM-5 OUD symptoms at baseline and past 30-day OUD symptoms at each follow-up. We assessed HIV risk with the Risk Assessment Battery (RAB), which generates three composite scores reflecting drug-related risk, sex-related risk, and overall HIV risk. Response options range from 0 to 7, with higher values reflecting greater risk. In addition, we assessed opioid use with urine drug screens (primarily collected from XR-NTX patients in medical management visits).

We scheduled these assessments to be administered at 1, 3, and 6, and 12 months following release. We asked participants who missed a scheduled follow-up interview to reconstruct prior periods of drug use and related behaviors at the subsequent appointment. As a result, contemporaneous follow-up rates were 71 (52.6%) at 1 month, 71 (52.6%) at 3 months, 90 (66.7%) at 6 months, and 112 (83.0%) at 12 months, whereas combined contemporaneous and reconstructed follow-ups were 127 (94.1%) at 1 month, 125 (92.6%) at 3 months, and 120 (88.9%) at 6 months (we reconstructed none of the 12-month interviews). We did not consider reconstructed responses missing.

We assessed dosing/protocol compliance and patient safety throughout the study via clinic records and reported adverse events.

2.5 Analysis plan

Primary analyses tested whether XR-NTX or XR-NTX+PN resulted in a lower proportion of participants with self-reported opioid use, a lower percentage of days using opioids, and fewer participants meeting criteria for current OUD (based on past 30 day symptoms) compared to ETAU at 1, 3, 6, and 12 months after being released from jail. We analyzed outcomes following intention-to-treat principles by including all available data regardless of the degree of exposure to the study interventions. We modeled outcomes using logistic and linear regression in R software version 3.6.1 (2019) to evaluate statistical significance and to estimate odds ratio (OR) and Cohen's d effect sizes (with Hedge's correction for small samples) of the two active treatments relative to ETAU. We still included participants with missing follow-up measures in outcome analyses by using multiple imputation, which estimates plausible values for missing outcome measures based on their observed associations with nonmissing baseline and follow-up measures (see Supplement). This method yields unbiased estimates when data are missing at random and reduces bias and produces more accurate confidence intervals even when data are not missing at random compared to complete-case analyses and imputation of single values (e.g., missing = relapse) (Hallgren & Witkiewitz, 2013; Hallgren et al., 2016); however, we also conducted supplemental analyses under the latter assumption that missing outcome data indicated opioid use. We obtained rearrest data through a statewide arrests database using personal identification numbers and we, therefore, considered all data complete.

3 Results

3.1 Screening and randomization

Of 333 potential participants screened, we excluded 18 due to pending additional charges, inability to understand informed consent, and other reasons related to eligibility factors. Of 315 participants who were consented, we did not randomize 164 due to early release, direct transfers to prison, or failed medical screens; and we randomized 151 (see Figure 1) using urn randomization balanced for gender. We provided field research staff with laptop computers with the randomization program installed. At the end of the consent and baseline assessment process, the research staff member pulled up the program, and entered the urn randomization variable—sex of the participant—showing the participant the computer screen as she entered the variables. Upon pressing “enter”, the randomization algorithm determined the treatment condition. Sixteen randomized patients were transferred directly to prison upon release from the index incarceration (and therefore were continuously incarcerated) and we, therefore, excluded them from analyses, leaving $N=135$ patients reported on here.

3.2 Descriptive statistics

Descriptive statistics at baseline are presented in Table 1. Participants were predominantly male, Hispanic, and white, with a mean age of 32.76 years. Just over half had a high school education or higher and just under a third were married, partnered, or in a long-term relationship. Most participants were homeless at the time of incarceration and 41% had been working full or part time. On average, participants reported using opioids on 27.58 (SD=7.08) out of the last 30 days before incarceration and endorsed 9.60 (SD=2.31) out of

11 OUD symptoms. There were no differences between study conditions on any baseline measures except baseline employment status, where a higher percentage of participants randomized to XR-NTX were working full or part time compared to ETAU and XR-NTX +PN. Additional analyses that adjusted for baseline employment did not yield substantively different conclusions, and the results presented here do not adjust for employment to facilitate easier interpretation. One participant is known to have died for reasons unrelated to the study (cancer) within 12 months of his release from jail.

3.3 Attendance, injections, and urine toxicology results at medication management visits

Participants in the XR-NTX condition attended a mean of 3.48 (SD=2.56) out of 10 possible medication management (MM) visits (see Table 2), including the baseline MM visit. On average, these participants had urine toxicology results that were negative for opioids and had no self-reported opioid use on 74% of visits (119 of 160). XR-NTX participants received a mean of 2.20 (SD=1.65) out of 7 possible injections, including the baseline injection and including five participants in this group (11%) who did not receive any injections (including the baseline injection) due to early release from jail ($n=2$) or due to refusing the first injection ($n=3$). Participants in the XR-NTX+PN condition attended a mean of 4.31 (SD=3.35) MM visits (see Table 2), including the baseline MM visit. On average, these participants had urine toxicology results that were negative for opioids and no self-reported opioid use on 71% of visits (137 of 194) and received 2.93 (SD=2.27) out of 7 possible injections, including the baseline injection. Across both conditions, only 8% of participants (7 of 91) received all seven possible injections, including three XR-NTX+PN participants (7%), who did not receive any injections (including the baseline injection) due to early release from jail ($n=2$) or due to refusing the first injection ($n=1$). The two medication conditions did not differ on any of these measures. Analysis of the PN contact log revealed a low participation rate for the XR-NTX+PN condition: out of 45 patients, 29 (64%) had no postrelease visits with the PN (though all met with the PN prior to release). The mean number of visits among the 16 people with at least one postrelease visit was 6.94 (SD=5.01).

3.4 Opioid use

3.4.1 Agreement between self-report and urine toxicology results—We verified self-reported opioid use based on urine toxicology reports when both reports were available at MM appointments (167 instances) and at follow-up assessments (43 instances; we requested urine specimens only from participants who came into the research center for their follow-up data collection session, which occurred for a minority of follow-up assessments). At MM sessions, 92% of cases (116 of 126) in which opioid use was denied during self-report also yielded negative urine toxicology results, and 34% of cases (14 of 41) in which opioid use was self-reported yielded positive urine toxicology results. Overall agreement between self-report and urine toxicology results at MM sessions was fair, with a Cohen's kappa of 0.60 (95% CI:0.45 to 0.74), indicating 60% agreement after controlling for agreement that would be expected by chance.¹ At follow-up assessments, in all 43 instances where urine toxicology and self-reports were both available, urine toxicology results were negative for opioids but two participants self-reported opioid use (95% agreement; Cohen's

kappa not computable due to a lack of positive urine toxicology results). Thus, overall, self-reports yielded higher rates of opioid use than urine toxicology.

3.4.2 Self-reported opioid use—Rates of any self-reported opioid use at 1, 3, 6, and 12-month follow-ups (primary outcome) are presented in Table 3. Across time points, most of the sample denied opioid use, with no differences between conditions at 1, 3, and 6 months. At 12 months, a significantly lower percentage of participants in the XR-NTX+PN condition (18%) reported opioid use compared to participants in ETAU (44%, OR=0.35, 95% CI: 0.13 to 0.99), but neither condition differed from XR-NTX (23%). Alternative analyses in which we considered all participants with missing follow-up data to be positive for opioid use yielded higher overall rates of opioid use at 1 month (44%), 3 months (28%), 6 months (30%), and 12 months (41%), with no differences between conditions including no difference between ETAU and XR-NTX+PN at 12 months ($p=.072$, see supplemental materials for more detailed presentation of these alternative analyses). Self-reported opioid use did not differ between XR-NTX and XR-NTX+PN.

3.4.3 Proportion of days using opioids—The percentage of days of self-reported opioid use is presented in Table 3. For the full sample, the percentage of days using opioids was 16% (1 month), 14% (3 months), 10% (6 months), and 14% (12 months). There were no differences between conditions on the proportion of days using opioids at any time point. When analyses were restricted to only include people who reported any opioid use at each follow-up, the percentage of days of self-reported opioid use was 55% ($n=36$ participants) at 1 month, 66% ($n=25$) at 3 months, and 86% ($n=18$) at 6 months. There were no differences between the conditions at 1 or 6 months for this subgroup of patients, but participants randomized to XR-NTX who reported using opioids had significantly lower percentage of days using opioids at 3-months (42%) compared to participants in ETAU (84%, $p=.03$) XR-NTX+PN (79%). Participants randomized to XR-NTX also had marginally but non-significantly lower percentage of days using opioids than participants in XR-NTX+PN (79%, $p=.07$).

3.4.4 OUD—The percentage of participants meeting criteria for OUD are shown in Table 3. Rates of OUD were low across the full sample at the 1-month (16%), 3-month (15%), 6-month (10%), and 12-month (14%) follow-ups. There were no differences between conditions on the rate of OUD at any follow-ups.

3.5 Secondary outcomes

3.5.1 HIV risk—Follow-up HIV risk scores are presented in Table 4. HIV risk did not differ between the treatment conditions for any of the time points, except at 12 months when participants in XR-NTX had significantly lower sex-related HIV risk than participants in ETAU (Cohen's $d=-0.45$, 95% CI: -0.83 to -0.07).

¹Patients denied opioid use in 126 MM sessions where urine toxicology results were also available; in 116 cases this was confirmed by opioid-negative toxicology results and in 10 cases participants had opioid-positive results. Patients reported opioid use in 41 MM sessions where urine toxicology results were also available; in 27 cases this was confirmed by opioid-positive toxicology results and in 14 cases participants had had opioid-negative results.

3.5.2 Recidivism—Rates of rearrest over the one-year period after release from the index incarceration are shown in Table 5. For the full sample, 56 of 135 participants (42%) were rearrested within one year after release. Of these, 44 participants (33% of full sample) had at least one felony arrest, and 17 (13% of full sample) had at least one arrest for a drug-related offense. There were no differences between conditions in rates of rearrest.

3.5.3 No incarceration or opioid use—Because patients who were incarcerated could have less access to opioids and therefore lower rates of self-reported opioid use, we also examined the proportion of participants who were simultaneously not incarcerated and reported no opioid use (see Table 6). For the full sample, 45 of 135 participants (35%) met these criteria at 1 month, 53 participants (42%) at 3 months, 39 participants (33%) at 6 months, and 29 participants (26%) at 12 months, with no differences between conditions.

3.6 Adverse events (AEs)

We assessed AEs for those in the two medication conditions who attended MM sessions. As a result, they likely represent an undercount. Among this subgroup, eight AEs were reported, including one nonfatal overdose. We deemed all other AEs to be mild in severity (two were deemed definitely drug related, three were deemed possibly drug related, and two were deemed not related to the study drug).

4 Discussion

Correctional settings offer an unparalleled opportunity for identifying and treating individuals with OUD (Rich et al., 2014). The importance of intervening with this population is widely acknowledged, but optimal strategies for delivering OUD interventions are still not well understood. The purpose of the current study was to assess the impact of XR-NTX, with and without the aid of a patient navigator, on postrelease opioid use and related outcomes.

Patients in the XR-NTX-PN condition showed nominally superior rates of clinic attendance and XR-NTX injections, but neither of these contrasts were statistically significant. Overall, treatment retention was low, with only 8 percent of patients receiving all seven possible injections. Low retention to XR-NTX among jail releases has been observed in other studies (Lincoln et al., 2018), and tends to be more problematic in actual practice than in prospective research studies (Jarvis et al., 2018). Self-reported opioid use was generally low and not different across the three groups at all follow-up time points, with the exception of the 12-month follow-up, during which XR-NTX+PN participants were less likely than ETAU participants to report any opioid use in the prior six months. This effect was not statistically significant when we assumed missing values indicated opioid use. Similarly, the percentages of participants meeting CIDI criteria for OUD were generally low at each of the four follow-up time points and did not differ by study condition. (We should note that the justice-involved participants in the Lee et al. [2016] study also showed a low overall rate of relapse to opioids over the 6-month follow-up, perhaps suggesting that the threat of reincarceration may have acted as a powerful incentive to stay abstinent.)

Analysis of secondary outcomes revealed a similar pattern, with no significant variation in arrests (operationalized as any arrest, any felony arrest, or any drug-related arrest), or HIV risk, with the exception of sex-related risk at the 12-month follow-up, which was lower among XR-NTX than ETAU participants.

This study had a number of strengths, including a randomized design; objective measures of XR-NTX adherence and rearrests; use of validated self-report measures such as the ASI, TLFB, and RAB; implementation in a real-world setting; and good follow-up rates.² However, achieving clarity in opioid use outcomes proved difficult due to the high rate of reincarcerations over the 12-month observation window—more than a third of those providing 1- and 3-month follow-up data, and more than half of those providing 6- and 12-month data had spent a portion of their reporting timeframes in jail or prison. This posed a challenge for collecting contemporaneous measures of drug use (whether from urine toxicology or self-report). To address this, we also calculated a “percentage of days used” measure that controlled for incarceration periods and also created a hybrid outcome measure that combined self-reported opioid use and reincarceration. Neither of these adjustments changed the overall patterns of the primary analyses. Although the subset of people who reported using opioids at 3 months had a lower percentage of days using in XR-NTX compared to ETAU and XR-NTX+PN, inferences around this finding are limited by the small sample included in this subgroup analysis (n=25 out of 135 enrolled).

A key potential limitation of this study is the lack of consistency in the collection of urine specimens across the full sample. We only collected urine specimens from participants in the medical management sessions (i.e., those receiving XR-NTX) or from participants who presented at the research center for their scheduled follow-ups. Our comparisons of self-reported opioid use versus urine toxicology results showed modest agreement ($Kappa=.60$), though self-reports tended to reveal more use than drug tests (in this study, self-reports covered 30- to 90-day reporting windows, while urines detect use in only the past 24–72 hours). However, as indicated here, across conditions a large proportion of the sample was reincarcerated at one or more of the follow-up points, which precluded us from collecting urine specimens. Although the evidence suggests that medications for OUD generally have only a modest impact on rearrest or reincarceration (Perry et al., 2015), reincarceration appears to have a large impact on our ability to evaluate the effects of medications for OUD. We endeavored to control for this by controlling for days of use as a percentage of nonincarcerated days, and also by creating a hybrid outcome where we operationalized “success” as reporting no opioid use and not being returned to custody.

The TLFB has been shown to produce valid estimates of drug use for up to one year (Robinson et al., 2014), arguably making the greatest threat to the internal validity of this study the high rates of reincarceration during the 12-month observation window, rather than the reliance on self-reports. Our attempts to control for this confound did not appreciably change the findings that neither opioid use nor the presence of OUD six months following release differed by study condition. Moreover, our objective measures showed that PN may

²The especially high follow-up rate at 12 months is unusual, and likely occurred because the research coordinators had more time to locate the participants, and because they offered a higher incentive at this time point.

have at best only a modest effect on XR-NTX treatment adherence, and that neither of the active treatment conditions produced lower likelihoods of rearrests.

The study also had a limited sample size. Because we ultimately deemed 16 of the randomized participants ineligible due to being transferred directly from jail to prison, the analyzable sample decreased from 151 to 135. This further reduced the statistical power of the study, which was originally designed to detect medium-to-large group differences.

The efficacy of XR-NTX on opioid use was likely hampered by low levels of treatment retention among participants in this study. The current study did not assess reasons for low adherence, but research has established that release from jail is a turbulent time in peoples' lives, during which individuals must re-establish housing, medical care, income, social lives, and attend probation appointments, all of which may compete with retention in treatment (Turner, 2018). Other logistical barriers, such as transportation, may also have played a role, especially given the wide catchment area and limited public transportation of Bernalillo County, New Mexico, where Albuquerque is located. We hypothesized that PN would help to overcome some of these barriers, but our findings did not support this hypothesis. Although there is limited evidence that wrap-around services reduce recidivism (Doleac, 2019), a more direct focus on medication adherence might reduce opioid use and improve associated postrelease outcomes. The lack of an observed effect of PN in this study may also be, in part, due to the participants' low rates of engagement with the patient navigator (nearly two thirds of the participants in this condition had no contact with the patient navigator following discharge, despite multiple contact attempts by the patient navigator). However, other rigorous studies of PN with SUD patients have produced similar null results, despite having relatively high levels of patient engagement. Using an experimental design, Metsch and colleagues (2016) assessed a PN intervention (alone vs. combined with financial incentives) to improve HIV-1 viral suppression rates among patients (N=801) with SUD and elevated HIV-1 viral loads. They found no differences in rates of HIV viral suppression or death across the conditions at 12 months, though they did find a modest additive beneficial effect of incentives and patient navigation at the 6-month time point while the intervention (incentives and navigation) were still active. In a more recent study, Schwartz and colleagues (2020) randomized arrestees (recruited in jail) with OUD to receive interim methadone alone, interim methadone coupled with PN, or enhanced treatment as usual. They found that significantly more participants in the interim methadone groups were in treatment 30 days after leaving jail (relative to ETAU), but the addition of PN did not improve drug use or treatment attendance outcomes. Future research should explore treatment delivery in places where recently incarcerated patients are likely to live or visit, such as halfway houses or probation offices. Many participants in the PN condition could not provide reliable contact information, or stated that they did not wish to be contacted in the community. Homelessness was also common among participants. Future research in this area should identify the factors and mechanisms that keep some patients engaged in XR-NTX and PN.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Use of extended-release naltrexone not associated with better outcomes among incarcerated adults with opioid use disorder.
- Patient navigation not associated with improved extended-release naltrexone adherence or opioid-use outcomes in a jail sample
- For justice-involved populations, measuring opioid-use outcomes is difficult due to the high rate of re-incarcerations—with the majority of the follow-up sample spending a portion of their reporting timeframes in jail or prison.

Fig. 1: CONSORT diagram.

Note: XR-NTX= Extended release naltrexone, PN = patient navigation, ETAU = enhanced treatment-as-usual.

Table 1

Participant demographics and opioid use at baseline.

	Full Sample (N = 135)	ETAU (N = 44)	XR-NTX (N = 46)	XR-NTX+PN (N = 45)
	n(%)	n(%)	n(%)	n(%)
Female	37(27%)	14(32%)	11(24%)	12(27%)
Age, <i>M</i> (<i>SD</i>)	32.76(9.37)	32.80(9.71)	31.37(9.54)	34.13(8.83)
Hispanic (any race)	87(64%)	27(61%)	30(65%)	30(67%)
White	94(70%)	26(59%)	36(78%)	32(71%)
Black/African American	12(9%)	6(14%)	3(7%)	3(7%)
American Indian	13(10%)	4(9%)	4(9%)	5(11%)
Other Race	5(4%)	2(5%)	1(2%)	2(4%)
Unknown Race	10(7%)	5(11%)	2(4%)	3(7%)
Married, partnered, or long-term relationship	44(33%)	12(27%)	20(43%)	12(27%)
High school education or higher	79(59%)	26(59%)	26(57%)	27(60%)
Working (full- or part-time)	56(41%)	15(34%)	27(59%)*	14(31%)
Homeless at time of incarceration	80(59%)	25(57%)	28(61%)	27(60%)
Baseline 30-day opioid use (ASI), <i>M</i> (<i>SD</i>)	27.58(7.08)	29.25(3.56)	27.00(7.92)	26.53(8.48)
Baseline OUD symptom count (CIDI), <i>M</i> (<i>SD</i>)	9.60(2.31)	9.70(2.15)	9.33(2.93)	9.78(1.69)
HIV risk, drug scale (RAB), <i>M</i> (<i>SD</i>)	5.59(5.26)	5.45(5.49)	5.20(5.02)	6.13(5.33)
HIV risk, sex scale (RAB), <i>M</i> (<i>SD</i>)	5.15(2.47)	5.05(2.36)	5.39(2.77)	5.00(2.27)
HIV risk, total (RAB), <i>M</i> (<i>SD</i>)	10.74(5.99)	10.50(5.95)	10.59(6.04)	11.13(6.09)
Duration of index incarceration, in days, <i>M</i> (<i>SD</i>)	143.91(86.32)	152.57(82.16)	141.96(92.01)	137.44(85.52)

Note. Differences for binary variables were evaluated using Fisher exact tests; differences for continuous variables were evaluated using *t*-tests.

* $p = 0.022$ (XR-NTX vs. ETAU) and $p = 0.011$ (XR-NTX vs. XR-NTX+PN).

Table 2

Attendance, injections, and opioid use at medication management (MM) visits.

	<u>XR-NTX</u>		<u>XR-NTX + PN</u>		<u>Difference</u>		
	M	(SD)	M	(SD)	d	(95% CI)	p-value
MM sessions attended	3.48	(2.56)	4.31	(3.35)	0.28	(-0.14, 0.69)	0.186
MM sessions with negative urine toxicology and no self-reported opioid use	2.59	(1.98)	3.04	(2.87)	0.18	(-0.23, 0.60)	0.38
Injections received	2.20	(1.65)	2.93	(2.27)	0.37	(-0.05, 0.79)	0.079

Note. Results above include the baseline MM session that occurred during incarceration. The number of post-release-only injections for XR-NTX and XR-NTX+PN are 1.2 (SD=1.7) and 1.9 (SD=2.3), respectively, $p = .08$.

Table 3

Opioid use and opioid use disorder outcomes.

	Any opioid use					Percentage of days using opioids						Opioid use disorder					
	n/N	%	OR *	(95% CI)	p *	M	(SD)	N	d *	(95% CI)	p *	n/N	%	OR *	(95% CI)	p *	
1 Month	ETAU	16/42	38%			15.04	(32.91)	39				7/39	18%				
	XR-NTX	17/41	41%	1.20	(0.48, 2.94)	0.69	19.55	(35.57)	40	0.14	(-0.34, 0.62)	0.54	7/41	17%	1.06	(0.33, 3.21)	0.92
	XR-NTX + PN	18/44	41%	1.16	(0.48, 2.77)	0.74	13.90	(31.81)	43	-0.10	(-0.59, 0.40)	0.74	5/41	12%	0.63	(0.19, 2.24)	0.46
3 Months	ETAU	11/42	26%			16.11	(31.80)	33				8/36	22%				
	XR-NTX	10/39	26%	1.12	(0.37, 2.81)	0.83	9.42	(28.24)	35	-0.17	(-0.75, 0.42)	0.66	4/36	11%	0.66	(0.17, 2.10)	0.53
	XR-NTX + PN	7/44	16%	0.57	(0.19, 1.62)	0.29	15.50	(34.93)	37	-0.11	(-0.72, 0.49)	0.80	5/41	12%	0.51	(0.15, 1.72)	0.27
6 Months	ETAU	7/41	17%			7.37	(19.83)	33				3/39	8%				
	XR-NTX	6/37	16%	1.15	(0.33, 3.93)	0.82	5.27	(18.56)	34	0.00	(-0.73, 0.73)	0.99	4/35	11%	1.91	(0.39, 8.80)	0.41
	XR-NTX + PN	12/42	29%	1.86	(0.66, 5.53)	0.25	17.09	(35.24)	38	0.18	(-0.49, 0.84)	0.53	4/39	10%	1.31	(0.30, 6.67)	0.74
12 Months	ETAU	17/39	44%			18.79	(32.00)	35				6/39	15%				
	XR-NTX	8/35	23%	0.47	(0.16, 1.35)	0.184	8.62	(24.58)	33	-0.16	(-0.84, 0.51)	0.58	2/35	6%	0.65	(0.14, 2.96)	0.56
	XR-NTX + PN	7/38	18%	0.35	(0.13, 0.99)	0.048	14.14	(33.37)	34	-0.10	(-0.71, 0.51)	0.69	7/37	19%	1.24	(0.39, 4.25)	0.72

* Effect sizes and p-values are obtained from the multiple imputation dataset and use ETAU as the reference condition.

Table 4

HIV risk outcomes.

	Total HIV Risk						Drug-Related HIV Risk						Sex-Related HIV Risk					
	<i>n</i>	<i>M</i>	<i>(SD)</i>	<i>d</i> [*]	(95% CI)	<i>p</i> [*]	<i>M</i>	<i>(SD)</i>	<i>d</i> [*]	(95% CI)	<i>p</i> [*]	<i>M</i>	<i>(SD)</i>	<i>d</i> [*]	(95% CI)	<i>p</i> [*]		
1 Month	ETAU	41	3.54	(3.46)			1.00	(2.48)				2.54	(1.69)					
	XR-NTX	41	4.20	(2.95)	0.12	(−0.29, 0.52)	0.57	0.88	(1.63)	−0.03	(−0.47, 0.41)	0.89	3.32	(1.93)	0.28	(−0.11, 0.67)	0.158	
	XR-NTX + PN	44	3.59	(4.13)	0.00	(−0.41, 0.42)	0.99	1.32	(3.19)	0.08	(−0.38, 0.54)	0.73	2.27	(1.47)	−0.11	(−0.48, 0.26)	0.56	
3 Months	ETAU	42	3.93	(4.50)			1.48	(3.37)				2.45	(1.71)					
	XR-NTX	39	3.36	(3.92)	−0.12	(−0.51, 0.28)	0.56	0.87	(2.18)	−0.13	(−0.56, 0.29)	0.54	2.49	(1.57)	−0.04	(−0.41, 0.32)	0.81	
	XR-NTX + PN	43	3.65	(4.83)	−0.07	(−0.46, 0.32)	0.74	1.40	(3.68)	−0.03	(−0.45, 0.38)	0.87	2.26	(1.75)	−0.10	(−0.47, 0.27)	0.58	
6 Months	ETAU	41	2.37	(1.71)			0.29	(0.98)				2.07	(1.54)					
	XR-NTX	37	3.00	(2.16)	0.23	(−0.25, 0.71)	0.34	0.35	(1.03)	0.13	(−0.44, 0.70)	0.65	2.65	(1.62)	0.23	(−0.17, 0.62)	0.26	
	XR-NTX + PN	42	2.79	(2.89)	0.15	(−0.31, 0.62)	0.51	0.76	(1.97)	0.25	(−0.30, 0.80)	0.37	2.02	(1.46)	0.00	(−0.39, 0.39)	0.99	
12 Months	ETAU	39	4.13	(3.84)			1.05	(2.35)				3.08	(2.12)					
	XR-NTX	35	2.91	(3.26)	−0.24	(−0.65, 0.16)	0.24	0.94	(2.63)	−0.02	(−0.46, 0.42)	0.92	1.97	(1.29)	−0.45	(−0.83, −0.07)	0.020	
	XR-NTX + PN	38	3.18	(3.88)	−0.18	(−0.60, 0.23)	0.39	0.84	(2.79)	−0.05	(−0.50, 0.41)	0.84	2.34	(1.88)	−0.30	(−0.68, 0.07)	0.113	

* Effect sizes and p-values are obtained from the multiple imputation dataset and use ETAU as the reference condition.

Table 5

Rearrests over one-year follow-up after release.

	Any Arrests					Any Felony Arrests					Any Drug Arrests				
	<i>n/N</i>	%	OR *	(95% CI)	<i>p</i> *	<i>n/N</i>	%	OR *	(95% CI)	<i>p</i> *	<i>n/N</i>	%	OR *	(95% CI)	<i>p</i> *
ETAU	18/44	41%				14 /44	32%				7 /44	16%			
XR-NTX	23/46	50%	1.44	(0.63, 3.35)	0.39	17 /46	37%	1.26	(0.53, 3.04)	0.61	7 /46	15%	0.95	(0.30, 3.02)	0.93
XR-NTX+PN	15/45	33%	0.72	(0.30, 1.71)	0.46	13 /45	29%	0.87	(0.35, 2.16)	0.76	4 /45	9%	0.52	(0.13, 1.85)	0.32

* Effect sizes and p-values are obtained from the multiple imputation dataset and use ETAU as the reference condition.

Table 6

No opioid use or incarceration.

		No opioid use or incarceration				
		<i>n</i> / <i>N</i>	%	OR [*]	(95% CI)	<i>p</i> [*]
1 Month	ETAU	19 / 42	45%			
	XR-NTX	14 / 41	34%	0.61	(0.25, 1.49)	0.27
	XR-NTX + PN	12 / 44	27%	0.46	(0.19, 1.13)	0.091
3 Months	ETAU	17 / 42	40%			
	XR-NTX	18 / 39	46%	1.13	(0.46, 2.75)	0.79
	XR-NTX + PN	18 / 44	41%	0.99	(0.42, 2.37)	0.99
6 Months	ETAU	12 / 41	29%			
	XR-NTX	16 / 37	43%	1.53	(0.60, 3.89)	0.37
	XR-NTX + PN	11 / 42	26%	0.80	(0.31, 2.11)	0.65
12 Months	ETAU	6 / 39	15%			
	XR-NTX	13 / 35	37%	2.47	(0.82, 7.40)	0.106
	XR-NTX + PN	10/38	26%	1.56	(0.49, 4.90)	0.45

* Effect sizes and p-values use ETAU as the reference condition.